2) In §2144.08 (f) (5) of the M.P.E.P., the Office is instructed to "specifically articulate what teachings or suggestions in the prior art would have motivated one of ordinary skill in the art to select the claimed species or subgenus." No such information was provided in the Office Action (explaining why it would be obvious to apply the stabilization technology developed for use with one molecule (rF-VIII) to stabilize IL-2).

3) A proper rejection of Claims 1-6, 9 and 10 under §103 has not been established. The first requirement to establish a prima facie case of obviousness under §103 was not met because the **location of any motivation to combine the references was not provided.** Secondly, the **Office Action is silent on** the source or location of any suggestion to combine **references that would provide a reasonable expectation of success** if the combination were to be made. MPEP § 2142

In Paper No. 8, the Patent Office replied to Applicant's comments by maintaining the earlier rejections under 35 USC 103 and providing the following two explanations:

1. "**Compounds to achieve protein stabilization**, such as sucrose, glycine, histidine, NaCl **do not have any particular preference to any protein. Their function is to inhibit/lower proteolytic activity and therefore they can be employed for stabilization of any protein and motivation is almost always there** for testing such possibility. A skilled artisan recognizes that one reason why a particular ingredient would be avoided in the protein stabilization mixture would be if it were needed in high enough concentration that even after several fold dilution, that ingredient would affect the processes that the stabilized polypeptide would be put to use." (Paper No. 8, Page 3, paragraph 1)

And,

2. "... **in all stabilization mixtures** (column 3, summary of the invention, lines 9 – end in U.S. Patent No. 5,874,408; column 2, summary of the invention, 3rd para, lines 5-end

of U.S. Patent No. 5,078,997; instant claim 9, ranges of sodium chloride and glycine concentrations) **each of the ingredients used are mentioned in what range they would be applicable, meaning that certain ingredients are also at '0' concentration.** The observed effects of such stabilizing mixtures when each ingredient is at its lowest concentration would provide the motivation for why any one component such as $CaCl_2$ should be eliminated. In fact, U.S. Patent No. 5,078,997 teaches that a stabilizer is selected from the group consisting essentially of: a mixture of arginine and carnitine ..., or mixtures thereof, ...' (column 2, summary of the invention, 2nd para, line 2 to the end of the paragraph)." (Paper No. 8, Page 3, paragraph 2)

Response to Rejection of Claims and Comments contained in Paper No. 8.

Paragraph 1 (above) **includes multiple errors of fact** that appear to have guided the determination that Claims 1-6, 9 and 10 in the present application are obvious under 35 U.S.C. § 103. **Paragraph 1** states that stabilizing agents serve to "inhibit/lower proteolytic activity and therefore they can be employed for stabilization of any protein and motivation is almost always is there for testing such possibility". This statement is incorrect and is unrelated to the clear teaching contained in the application or any prior art reference.

The term "stabilized" is defined on page 5 of the specification, and on the same page the related concept of **aggregation** is introduced. The fact that aggregation is a major mechanism of instability in IL-2 is discussed on page 11. The inventors' belief that aggregation is associated with free –SH groups on Cys^{125} reacting with disulfide bonds via the thiol/disulfide exchange pathway, resulting in aggregation/ precipitation events, is also discussed on page 11. On page 12, the inventors discuss the role of histidine in the stabilizing mixture. Therapeutic proteins are complex molecules, and contrary to the statement contained in the Office Action, **it is not well known that any stabilizer can be employed for stabilization of any protein.** Rather, **the development of stabilized peptides is necessitated by the aggregation of peptides, produced by binding events that cause the precipitation of the peptide from solution.** The development of

stabilization mixtures is driven in major part by the composition of the target protein, its amino acid composition, pH, and conformation. **The comment contained in the Office Action is unrelated to the stabilization technology disclosed throughout Applicant's specification, or any cited reference.** Moreover, **the purpose of protein stabilization is not intended to inhibit/lower proteolytic activity**; and there is no apparent support for the Office Action's statement in the scientific literature.

In Paragraph 2, the Office Action refers to the Summary of Invention in two issued patents and then states, "**each of the ingredients used are mentioned in what range they would be applicable, meaning that certain ingredients are also at 'o' concentration".**

The two patents mentioned are: 5,874,408 and 5,078,997.

In relevant parts:

> The Summary portion of the '408 patent states: "The formulation **comprises** ... the following ingredients:
>
> Histidine up to about 50 mM, and
> CaCL up to about 5 mM
>
> The Summary portion of the '997 patent states: " The present invention more specifically **comprises** a composition that is stable, sterile, and soluble in aqueous medium .... No component listed in this patent has a '0' concentration.

MPEP § 2111.03 states in paragraph 2 that the term "**comprising" is a term of art** used in claim language **which means that the named elements are essential**; but other elements may be added. In the '408 patent, the range referred to in the Office Action is stated to **comprise "up to about 50 mM" of histidine and up to about 5 mM CaCl. Because the term "comprising" is used, each element must be present in the '408 preparation; and therefore no element may be present at a zero concentration** (as is suggested in the Office Action). This analysis is further supported by the disclosure in the '408 patent. Therefore, for the reasons stated above, **the '408 invention does not**

provide motivation for someone to eliminate components (CaCl or rFactor VIII) **of the mixture to make the invention of the present application.**

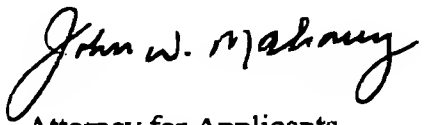
It is unclear what the Office Action intends by its comments regarding the teachings of the '997 patent.

Summary and Conclusion:

Applicant's invention is not obvious in light of the teachings contained in the Office Action. No prior art document teaches or suggests Applicant's stabilizing mixture. Applicants believe that the comments contained in Paper No. 8 are neither based upon an objective review of the facts nor responsive to Applicant's comments in Paper No. 7.

With the pending application and claims, Applicants' have met each of the requirements for receiving patent protection on their technology. In light of the comments presented above, applicants request that the Office withdraw its rejections under §103. Applicants believe that Claims 1-6, 9 and 10 are in condition for allowance, and each of the grounds of objection and rejection has been addressed, and prompt issuance of the present case is earnestly solicited.

Respectfully Submitted,



Attorney for Applicants
John W. Mahoney
Reg. No. 44, 892

Bayer Corporation
Law and Patent Department
800 Dwight Way
P.O. Box 1986
Berkeley, CA 94701-1986
(510) 705-7725